

Atty. Dkt. No. 059314-0401
Appl. No. 10/534,579

Amendments to the Specification

Please amend the specification as follows:

On page 1, please replace the paragraph underneath the title with the following rewritten paragraph:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is the National Phase Application of International Application No. PCT/US03/35946, filed on November 10, 2003, which claims the benefit of U.S. Provisional Applications Nos. 60/426105, filed November 13, 2002; 60/433215, filed December 12, 2002; 60/453127, filed March 7, 2003; 60/454801, filed March 13, 2003; 60/465619, filed April 24, 2003; 60/465495, filed April 24, 2003; and 60/491800, filed August 1, 2003.

Please replace the paragraph beginning at page 1, line 11, with the following rewritten paragraph:

Lipids are water-insoluble, oily or greasy substances that are soluble in nonpolar solvents such as chloroform or ether. Neutral fats (triacylglycerols) serve as major fuels and energy stores. Fatty acids are long-chain organic acids with a single carboxyl group and a long non-polar hydrocarbon tail. Long-chain fatty acids are essential components of glycolipids, phospholipids, and cholesterol, which are building blocks for biological membranes, and of triglycerides, which are biological fuel molecules. Lipids, such as phospholipids, sphingolipids, glycolipids, and cholesterol, are key structural components of cell membranes. Lipids and proteins are associated in a variety of ways. Glycolipids form vesicles that carry proteins within cells and cell membranes. Interactions between lipids and proteins function in targeting proteins and glycolipids involved in a variety of processes, such as cell signaling and cell proliferation, to specific membrane and intracellular locations. Various proteins are associated with the biosynthesis, transport, and uptake of lipids. In addition, key proteins involved in signal transduction and protein targeting have lipid-derived groups added to them post-translationally (Stryer, L. (1995) Biochemistry, W.H. Freeman and Co., New York N.Y., pp.

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264-267, 934; Lehninger, A. (1982) Principles of Biochemistry, Worth Publishers, Inc. New York N.Y.; and ExPASy "Biochemical Pathways" index of Boehringer Mannheim World Wide Web site; "~~<http://www.expasy.ch/cgi-bin/search-biochem-index>~~".)

Please replace the paragraph beginning at page 2, line 26, with the following rewritten paragraph:

The phosphatidylinositol-transfer protein Sec14, which catalyses exchange of phosphatidylinositol and phosphatidylethanolamine between membrane bilayers in vitro, is essential for vesicle budding from the Golgi complex. Sec14 includes a carboxy-terminal domain that forms a hydrophobic pocket which represents the phospholipid-binding domain. (Sha, B. et al. (1998) Nature 391:506-510). Sec14 is a member of the cellular retinaldehyde-binding protein (CRAL)/Triple function domain (TRIO) family (InterPro Entry IPR001251, ~~<http://www.ebi.ac.uk/interpro>~~).

Please replace the paragraph beginning at page 13, line 8, with the following rewritten paragraph:

A variety of lipolytic enzymes with a GDSL-like motif as part of the active site have been identified. Members of this family include a lipase/acylhydrolase, thermolabile hemolysin and rabbit phospholipase (AdRab-B)(Interpro entry IPR001087; ~~<http://www.sanger.ac.uk>~~). A homolog of AdRab-B is guinea pig intestinal phospholipase B, a calcium-independent phospholipase that contributes to lipid digestion as an ectoenzyme by sequentially hydrolyzing the acyl ester bonds of glycerophospholipids. Phospholipase B also has a role in male reproduction (Delagebeaudeuf, C. et al. (1998) J. Biol. Chem. 273:13407-13414).

Please replace the paragraph beginning at page 33, line 24, with the following rewritten paragraph:

Alternatively, a suite of commonly used and freely available sequence comparison algorithms which can be used is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S. F. et al.

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(1990)J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, Md., and on the Internet at nebi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at nebi.nlm.nih.gov/blast2.html. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (Apr. 21, 2000) set at default parameters. Such default parameters may be, for example:

Please replace the paragraph beginning at page 82, line 15, with the following rewritten paragraph:

Transcript-images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity (Nuwaysir, E. F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N. L. Anderson (2000) Toxicol. Lett. 112-113:467-471). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene

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function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity (see, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released Feb. 29, 2000, ~~available at niehs.nih.gov/oc/news/toxchip.htm~~). Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

Please replace the paragraph beginning at page 91, line 18, with the following rewritten paragraph:

Map locations are represented by ranges, or intervals, of human chromosomes. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Genethon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" ~~World Wide Web site~~ (~~ncbi.nlm.nih.gov/genemap/~~), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.